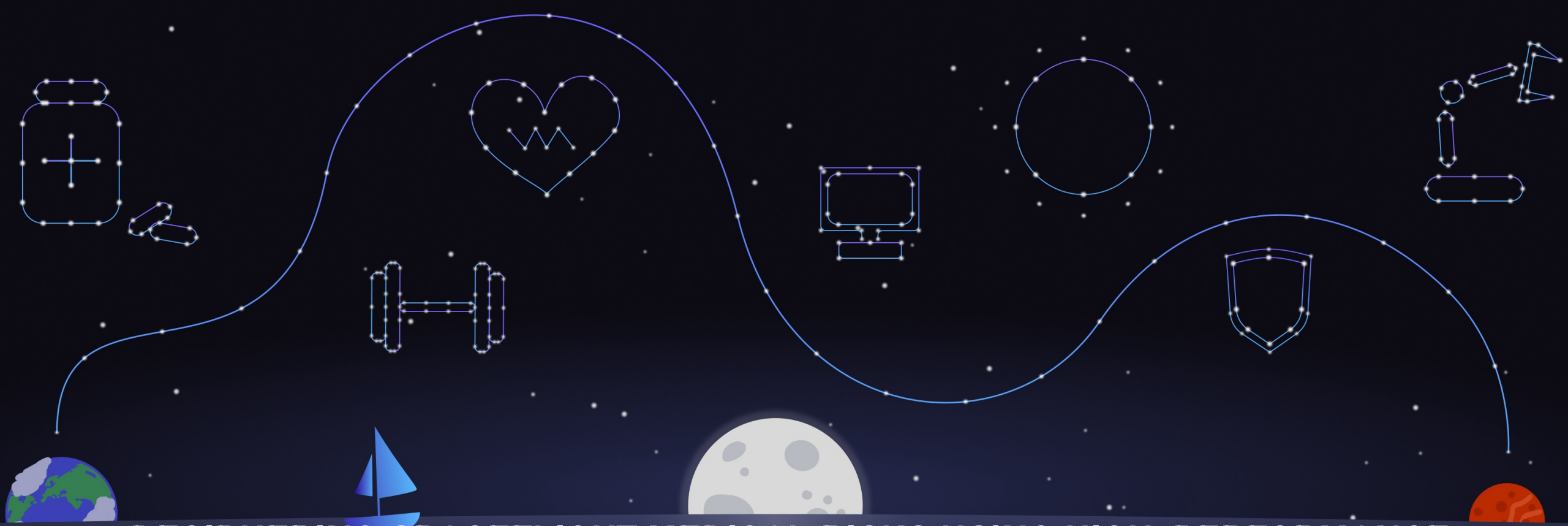

DECIPHERING SPACEFLIGHT MEDICAL RISKS USING HIGH-PERFORMANCE COMPUTING AND NEXT GENERATION SEQUENCING DATA FROM MODEL ORGANISMS

V. Stolc[1] M. Karhanek[2] and D. J. Loftus[1]
[1]NASA Ames Research Center (viktor.stolc-1@nasa.gov), [2]KBR Wyle

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Introduction:

- Unlike inherited mutations, low frequency **somatic mutations** of the genome accumulate over the lifetime of an organism.
- With the advent of next generation sequencing (NGS), the whole genome or the whole exome can be sequenced quickly, in order to study somatic mutations.
- Over the last 15 years, NGS-enabled studies of somatic mutations have shed light on the development of pre-cancerous conditions, cancer, inflammatory processes and degenerative diseases, all relevant to deep space travel.
- In this poster presentation, we present a study of somatic mutation in mice flown to the ISS, using data archived in GeneLab.
- Our results show rapid accumulation of somatic mutations in the spaceflight animals, in all tissues examined, compared to ground controls.

Method:

16 wk. old, female, C57BL/6J,
18 wk. old, female, BALB/c

→ 37-42d, Rodent Habitat, **ISS** → Euthasol, CD, -80° C → Thaw, Dissection → Kidney, Skeletal muscle, Eye, Liver (n = 72 each)

→ 37-42d, Rodent Habitat, **Ground** → Euthasol, CD, -80° C → Thaw, Dissection → Kidney, Skeletal muscle, Eye, Liver (n = 72, each)

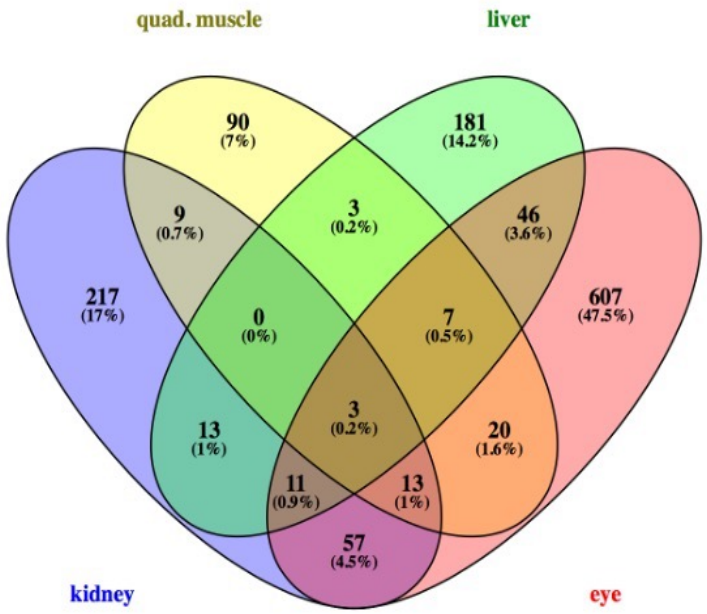
RNA sequencing library construction done at UC Davis.

Illumina HiSeq 4000

Sequence variants determined by a novel analytical pipeline developed at NASA Ames Research Center.

Results:

Tissue	Variants	unique SNVs	unique NSMs	unique(NSMs/SNVs)
GLDS-162 (eye)	94755	67200	22865	34.03%
GLDS-137 (liver)	50701	31366	6516	20.77%
GLDS-102 (kidney)	48577	30430	9780	32.14%
GLDS-103 (quad muscle)	43883	26127	7722	29.56%



- Using a novel analytical pipeline and high-performance computing resources, mutations in kidney, skeletal muscle (quadriceps), liver and eye tissue were observed in mice flown aboard the ISS.
- The results are highly statistically significant (data not shown).
- Essentially no mutations were observed in the same tissues in the ground control animals.
- The Venn diagram indicates the numbers of genes mutated in the various tissues, some of which were unique to the individual tissues, and some of which were shared among tissues.

Summary and Next Steps:

- We have discovered a high rate of somatic mutations in various tissues from mice that spent approximately 5-6 weeks in space aboard the ISS.
- Non-synonymous mutations (mutations that affect the amino acid sequence of the proteins) amounted to approximately 1/4 to 1/3 of all mutations observed.
- Many aspects of the spaceflight environment that the animals experienced aboard the ISS may have contributed to the observed increase in somatic mutation rate, including weightlessness, stress, and elevated carbon dioxide levels aboard the ISS.
- Elevated Reactive Oxygen Species (ROS) may be a significant biochemical explanation to account for the increased mutation rate.
- Space radiation exposure, by itself, cannot account for the increased rate of accumulation of somatic mutations, based on terrestrial studies of radiation-induced somatic mutation in humans where radiation is the primary independent variable.
- Although the physiological implications of the observed somatic mutations are not clear, it's likely that these genomic changes have an impact on known spaceflight degenerative processes.
- These findings highlight the need for studies of somatic mutation in crew members who travel to the ISS and beyond.